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Endoscopic cyclophotocoagulation (ECP) for open angle glaucoma and primary angle closure (Protocol)

Tóth M, Hu K, Bunce C, Gazzard G

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Endoscopic cyclophotocoagulation (ECP) for open angle glaucoma and primary angle closure

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The main objective is to assess the results at two years of ECP for OAG and primary angle closure in comparison to conventional medical, laser, or surgical treatment, in terms of efficacy and safety. A secondary objective will be to examine the effect of the effects of ECP treatment with concomitant phacoemulsification in comparison to ECP treatment alone.

BACKGROUND

This protocol is based on the protocol from the published review on ab interno trabecular bypass surgery with Trabectome for open angle glaucoma (Hu 2016).

Description of the condition

Glaucoma is a progressive optic neuropathy, affecting 3.5% of people aged 40 to 80 years (Tham 2014). It is the leading cause of irreversible blindness, affecting over 64 million people globally (Tham 2014). This figure is expected to increase to 110 million people by 2040. Open angle glaucoma (OAG) is the commonest type, accounting for 86% of cases (Tham 2014). In one large population cohort, one in six people with OAG became bilaterally blind (Peters 2013). Angle closure glaucoma is less common than OAG, but is more likely to result in bilateral blindness. The only proven way to prevent vision loss is to reduce the

pressure inside the eye (intraocular pressure (IOP)) over the long term (AGIS 2000; CNTG Study Group 1998; Heijl 2002; Kass 2002). Approaches to reducing IOP include medical therapy, laser treatments, and surgery. Because commercially available eye-drop preparations have a short-lasting effect, medical therapy requires eye-drops to be instilled one or more times daily for life. Adherence is very poor, even if use is monitored (Friedman 2009; Okeke 2009). Conventional surgical techniques, such as trabeculectomy, are associated with significant risks, with more than 40% of people developing perioperative complications (Kirwan 2013; Lichter 2001) and reoperation being needed in 7% to 18% (Gedde 2012; Kirwan 2013). Therefore, they are often reserved for disease that is progressing despite other treatments (King 2013).

Description of the intervention

In the past years, a number of minimally-invasive surgical techniques have been developed with the aim of achieving long-term reduction of IOP with a better safety profile than conventional surgery (Francis 2011a). Among them, endoscopic cyclophotocoagulation (ECP) is a cyclodestructive procedure developed by Martin Uram in 1992 (Uram 1995).

How the intervention might work

The ciliary body is the site of aqueous humour production. In cyclodestructive procedures, the secretory epithelium of the ciliary epithelium is damaged, which leads to reduced aqueous humour secretion and lower IOP. Endoscopic cyclophotocoagulation incorporates a diode laser, an aiming beam and video camera imaging. Direct visualisation of the ciliary endothelium allows the delivering of energy precisely to the ciliary processes in a highly titratable fashion, while minimizing collateral damage to the surrounding tissue.

Why it is important to do this review

Consultation with patients and healthcare professionals has identified a need for better treatments for glaucoma (James Lind Alliance 2013). Minimally-invasive glaucoma surgeries (MIGS) carry the possibility of safe and effective long-term reduction of IOP, removing concerns about permanent vision loss due to nonadherence to eye-drops. A single treatment may also be more acceptable to patients than daily and indefinite self-administration of eye-drops. Initial results of ECP were reported in 1992 by Uram (Uram 1992), where he treated 10 eyes with neovascular glaucoma. Since then, several studies have demonstrated the IOP-lowering effect of ECP in different glaucoma forms (Chen 1997; Francis 2011b; Lima 2004). In the light of the potential benefits for patients and the widespread uptake of the technique, it is important to critically evaluate the evidence for the efficacy and safety of ECP treatment. Importantly, ECP may be combined with phacoemulsification (cataract surgery), a sight-restoring operation to remove the natural lens of the eye when it has lost clarity. Since phacoemulsification itself reduces IOP (Mansberger 2012), we will specifically examine the evidence for the efficacy of ECP when combined with phacoemulsification in comparison to phacoemulsification alone. This Cochrane review will be conducted in parallel with other reviews currently undertaken by the Cochrane Eyes and Vision MIGS Consortium, which includes minimally-invasive glaucoma surgery (MIGS) techniques and devices such as the Trabectome (NeoMedix, Tustin, California) (Hu 2016), Hydrus Schlemm's canal Microstent (Ivantis Inc., Irvine, California) (Otarola 2017), XEN Glaucoma Implant (AqueSys Implant, Aliso Viejo, California) and iStent or iStent inject (Glaukos Corporation, Laguna Hills, California).

OBJECTIVES

The main objective is to assess the results at two years of ECP for OAG and primary angle closure in comparison to conventional medical, laser, or surgical treatment, in terms of efficacy and safety. A secondary objective will be to examine the effect of the effects of ECP treatment with concomitant phacoemulsification in comparison to ECP treatment alone.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) only. We will include reports of RCTs prepared in any language, irrespective of their publication status.

Types of participants

Participants will have OAG of any type, including primary and secondary OAG, or primary angle closure with raised IOP with or without glaucoma (PAC-OHT or PACG). Secondary forms of angle closure will be excluded. As there are no universally-accepted criteria by which glaucoma may be defined, we will permit studies to use their own definitions of glaucoma. In addition, participants with ocular hypertension, normal tension glaucoma, or possible glaucoma (suspects for glaucoma) will be included. We will not apply any restrictions regarding location, setting, or demographic factors.

Types of interventions

The intervention will be ECP. Although it is possible to deliver variable degrees of treatment on the ciliary body with titratable power levels, we will not apply any particular inclusion or exclusion criteria around these or other treatment delivery parameters. There are two main approaches to reach ciliary body: via limbal or pars plana entry. As the latter requires anterior vitrectomy, it cannot be considered as MIGS, and will not be part of this review.

We will compare ECP to:

1. laser treatment (selective laser trabeculoplasty or argon laser trabeculoplasty);
2. other MIGS techniques;
3. conventional glaucoma surgery (trabeculectomy)
4. medical therapy; or
5. in combination with phacoemulsification compared with phacoemulsification alone (since phacoemulsification cataract surgery is known to reduce IOP (Mansberger 2012)).

Types of outcome measures

We will not use the reporting of particular outcomes as a criterion for eligibility for review. We will not exclude studies from review solely on the grounds of an outcome of interest not being reported.

Primary outcomes

The primary outcome will be the proportion of participants who are drop-free (not using eye drops) at two years after randomisations.

Several different glaucoma outcome measures have been specified as primary outcomes in other Cochrane Reviews and protocols (Ismail 2015). A recent study classified IOP, visual field, safety, and anatomic outcomes as being highly important to glaucoma experts (Ismail 2016). A panel of patients from the Patient and Public Involvement Group of the National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology identified drop-free disease control as a highly-valued outcome (unpublished). We chose a participant-centred primary outcome. In assessing this outcome, we will report how prescribing of IOP-lowering eye drops was determined during follow-up. We will examine whether the people measuring IOP and those deciding upon the prescribing of IOP-lowering eye drops were masked to treatment group.

Secondary outcomes

Secondary outcomes will be:

1. Mean change in IOP, measured using Goldmann applanation tonometry, from randomisations to two years.
2. The proportions of participants experiencing intra- and postoperative complications from randomisations to two-year follow-up including but not restricted to the following:
 - Loss of visual acuity (more than two Snellen lines or more than 0.3 logMAR, according to the method of recording visual acuity; or loss of light perception).
 - Bleeding, as recorded by the investigators.
 - Endophthalmitis, as recorded by the investigators.
 - IOP spikes (postoperative rise in IOP, measured using Goldmann applanation tonometry, of more than 10 mmHg compared to the previous assessment, including during the first postoperative month).
 - Hypotony (significant postoperative reduction of IOP to 6 mmHg or below).
 - Phthisis bulbi, as recorded by the investigators.
 - Secondary surgery, as recorded by the investigators.
3. Change from randomisations to two-year follow-up in health-related quality of life measure.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no language or publication year restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) (Appendix 1);
- MEDLINE Ovid (1946 to present) (Appendix 2);
- Embase Ovid (1980 to present) (Appendix 3);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch) (Appendix 4);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 5);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictpr) (Appendix 6).

Searching other resources

We will search the reference lists of included studies for other possible studies and will contact any individuals or organisations whom we believe may have conducted or be conducting relevant RCTs. We will also search the website of the manufacturer (Endo Optiks, Little Silver, NJ, USA: endooptiks.com) for any information on forthcoming trials.

Data collection and analysis

Selection of studies

Two review authors working independently will screen titles and abstracts of all articles identified by the search using web-based review management software (Covidence 2015). If abstracts are not available, we will screen full-text articles. Two review authors will independently assess full-text reports of all potentially eligible studies. If there is disagreement regarding eligibility, a third review author will arbitrate. If any full-text reports are rejected, we will record the reasons for this.

Data extraction and management

We will extract data from reports of included studies using a data collection form, which will be developed and piloted on the first five studies included. Two review authors will work independently to extract study characteristics from reports of each study and enter the data into Review Manager 5 (RevMan 5) (Review Manager 5 2014). If there is disagreement, a third review author will arbitrate. We will collect the following information on the characteristics of included studies (Appendix 7):

- Year of publication.
- Year of study.
- Country of study.
- Sample size.
- Participation rate.
- Method of recruitment.
- Eligibility criteria.
- Diagnostic criteria.
- Method of randomisations.
- Method of masking.
- Number of study arms.
- Types of participants.
- Types of interventions.
- Types of comparators.
- Use of phacoemulsification at the same time as the

intervention.

We will collect the following data regarding outcomes (Appendix 7):

- IOP at baseline.
- IOP at follow-up.
- Number of glaucoma medications at baseline.
- Number of glaucoma medications at follow-up.
- Intraoperative complications.
- Postoperative complications or secondary surgery.
- Duration of follow-up.
- Loss to follow-up.
- Intervals at which outcomes were assessed.

Where data on included studies are missing or unclear, we will contact the individuals or organisations involved to obtain clarification. We will collect and use the most detailed numerical data available to facilitate analyses of included studies. We will attempt to obtain these data from individuals or organisations in preference to less precise methods such as extracting numeric data from graphs. If this is necessary, two review authors will independently extract the data and a third review author will arbitrate in case of disagreement.

Assessment of risk of bias in included studies

We will use the latest version of the Cochrane 'Risk of bias' tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess the risk of bias and assign judgements of this for included studies.

Measures of treatment effect

The primary outcome is the proportion of participants who are drop-free two years after randomisations. We will use the risk ratio as the measure of effect for this outcome.

We will report mean change in IOP from randomisations to two years after randomisations. Secondary safety outcomes will be reported as risk ratios. Health-related quality of life outcomes will

be reported as differences in means or risk ratios for continuous and binary data, respectively.

Unit of analysis issues

We will assess whether included studies have included one or two eyes from each participant and whether or not randomisations has been conducted at the level of the participant or the eye. There is a potential for medical treatments, such as topical beta blockers, used for one eye to influence the outcome in the other eye (Piltz 2000). Surgery to lower IOP in one eye may also affect the IOP of the fellow eye (Radcliffe 2010). Therefore, we will exclude studies that have adopted a paired design.

Dealing with missing data

We will endeavour to minimize missing outcome data by contacting individuals and organisations to obtain them. If the data are unavailable, but the level of missing data in each group and reasons for missing data in each group are similar, we may simply analyse available case data if an intention-to-treat (ITT) analysis has not been performed. If authors have conducted their own ITT analysis despite missing data, we will document whether they provide any justification for the method they have used to deal with missing data and whether they have compared their ITT result with an available case result.

Assessment of heterogeneity

We will assess the heterogeneity between trials by careful examination of the study reports, assessing forest plots, and an examination of the I^2 value. We will consider I^2 values greater than 50% as indicative of substantial heterogeneity and, therefore, suggestive that meta analysis might not be wise; however, we will give consideration to the consistency of the effect estimates. If all estimates are in the same direction, we might meta-analyse even where heterogeneity is evident; we will comment on the heterogeneity.

Assessment of reporting biases

We will use a funnel plot to assess the risk of publication bias if there are more than 10 trials within our review.

Data synthesis

We will undertake a meta-analysis where data appear clinically, methodologically, and statistically homogeneous. We will check that participants, interventions, comparators, and outcomes are sufficiently similar to give a clinically meaningful result and that our I^2 result indicates little inconsistency (i.e. I^2 less than 50%). If all estimates are in the same direction, we might meta-analyse even where heterogeneity is evident, but will comment on this. We

will use a random-effects model unless there are fewer than three eligible studies, in which case we will use a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We will undertake a subgroup analysis. The effect modifier to be examined will be use of phacoemulsification as a co-intervention. Phacoemulsification has been shown to reduce IOP (Mansberger 2012). We will therefore analyse whether the effect of ECP surgery differs depending on whether phacoemulsification is used as a co-intervention.

Sensitivity analysis

We will assess the impact of including studies at high risk of bias for an outcome in one or more key domains.

Summary of findings

We will prepare tables to summarise the findings of the review, including the assessment of the quality of evidence for all outcomes using the GRADE approach (GRADEpro 2014). All outcomes considered in the review will be reported in the summary. We will report the following outcomes in the 'Summary of findings' table and the comparison groups described under [Types of interventions](#): ECP compared with laser treatment, other

MIGS techniques, conventional glaucoma surgery (trabeculectomy), medical therapy or in combination with phacoemulsification compared with phacoemulsification alone.

1. Proportion of participants who are drop-free (not using eye drops) at two years follow-up.
2. Mean change in number of IOP-lowering drops taken per day from baseline to two years follow-up.
3. Mean change in IOP, measured using Goldmann applanation tonometry, from baseline to two years follow-up.
4. Health-related quality of life at two years follow-up.
5. Intraoperative complications.
6. Postoperative complications up to two years follow-up.
7. Secondary glaucoma surgery, including laser, as recorded by the investigators of the included trials between baseline and two years follow-up.

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Radcliffe NM, Musch DC, Niziol LM, Liebmman JM, Ritch R, Collaborative Initial Glaucoma Treatment Study Group. The effect of trabeculectomy on intraocular pressure of the untreated fellow eye in the collaborative initial glaucoma treatment study. *Ophthalmology* 2010; **117**(11):2055–60.

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* Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
- #2 MeSH descriptor: [Intraocular Pressure] explode all trees
- #3 MeSH descriptor: [Ocular Hypertension] explode all trees
- #4 OAG or POAG or IOP or OHT
- #5 simple near/3 glaucoma*
- #6 open near/2 angle near/2 glaucoma*
- #7 chronic near/2 glaucoma*
- #8 secondary near/2 glaucoma*
- #9 low near/2 tension near/2 glaucoma*
- #10 low near/2 pressure near/2 glaucoma*
- #11 normal near/2 tension near/2 glaucoma*
- #12 normal near/2 pressure near/2 glaucoma*
- #13 pigment near/2 glaucoma*
- #14 MeSH descriptor: [Exfoliation Syndrome] this term only
- #15 exfoliat* near/2 syndrome*
- #16 exfoliat* near/2 glaucoma*
- #17 pseudoexfoliat* near/2 syndrome*
- #18 pseudoexfoliat* near/2 glaucoma*
- #19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
- #20 endoscop* near/2 cyclophotocoagulat*
- #21 ECP
- #22 #20 or #21
- #23 #19 and #22

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle/
14. exp intraocular pressure/
15. ocular hypertension/
16. (OAG or POAG or IOP or OHT).tw.
17. (simple\$ adj3 glaucoma\$).tw.
18. (open adj2 angle adj2 glaucoma\$).tw.
19. (primary adj2 glaucoma\$).tw.
20. (chronic adj2 glaucoma\$).tw.
21. (secondary adj2 glaucoma\$).tw.
22. (low adj2 tension adj2 glaucoma\$).tw.
23. (low adj2 pressure adj2 glaucoma\$).tw.
24. (normal adj2 tension adj2 glaucoma\$).tw.
25. (normal adj2 pressure adj2 glaucoma\$).tw.
26. (pigment\$ adj2 glaucoma\$).tw.
27. exfoliation syndrome/
28. (exfoliat\$ adj2 syndrome\$).tw.
29. (exfoliat\$ adj2 glaucoma\$).tw.
30. (pseudoexfoliat\$ adj2 syndrome\$).tw.
31. (pseudoexfoliat\$ adj2 glaucoma\$).tw.
32. or/13-31
33. (endoscop\$ adj2 cyclophotocoagulat\$).tw.
34. ECP.tw.
35. 33 or 34
36. 32 and 35
37. 12 and 36

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by [Glanville 2006](#).

Appendix 3. EMBASE Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9

11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. open angle glaucoma/
34. intraocular pressure/
35. intraocular hypertension/
36. (OAG or POAG or IOP or OHT).tw.
37. (open adj2 angle adj2 glaucoma\$).tw.
38. (primary adj2 glaucoma\$).tw.
39. (chronic adj2 glaucoma\$).tw.
40. (secondary adj2 glaucoma\$).tw.
41. (low adj2 tension adj2 glaucoma\$).tw.
42. (low adj2 pressure adj2 glaucoma\$).tw.
43. (normal adj2 tension adj2 glaucoma\$).tw.
44. (normal adj2 pressure adj2 glaucoma\$).tw.
45. (pigment\$ adj2 glaucoma\$).tw.
46. exfoliation syndrome/
47. (exfoliat\$ adj2 syndrome\$).tw.
48. (exfoliat\$ adj2 glaucoma\$).tw.
49. (pseudoexfoliat\$ adj2 syndrome\$).tw.
50. (pseudoexfoliat\$ adj2 glaucoma\$).tw.
51. or/33-50
52. (endoscop\$ adj2 cyclophotocoagulat\$).tw.
53. ECP.tw.
54. 52 or 53
55. 51 and 54
56. 32 and 55

Appendix 4. ISRCTN search strategy

endoscopic cyclophotocoagulation OR ECP

Appendix 5. ClinicalTrials.gov search strategy

endoscopic cyclophotocoagulation

Appendix 6. ICTRP search strategy

endoscopic cyclophotocoagulation

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	<ul style="list-style-type: none">· Parallel group RCT <i>i.e. people randomised to treatment</i>· Within-person RCT <i>i.e. eyes randomised to treatment</i>· Cluster RCT <i>i.e. communities randomised to treatment</i>· Cross-over RCT· Other, specify	<ul style="list-style-type: none">Number of study armsMethod of randomisationExclusions after randomisationLosses to follow-upNumber randomised/analysedMethod of maskingHow were missing data handled? <i>e.g. available case analysis, imputation methods</i>Reported power calculation (Y/N), <i>if yes, sample size and power</i>Unusual study design/issues
Eyes Unit of randomisation/ unit of analysis	<ul style="list-style-type: none">· One eye included in study, <i>specify how eye selected</i>· Two eyes included in study, both eyes received same treatment, <i>briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture of one eye and two eyes</i>· Two eyes included in study, eyes received different treatments, <i>specify if correct pair-matched analysis done</i>	
Participants		
Country		<ul style="list-style-type: none">SettingEthnic groupMethod of recruitmentParticipation rateEquivalence of baseline characteristics (Y/N)

(Continued)

Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are reported for the people who were followed up only, please indicate.</i>	
Number (%) of men and women		Number (%) of men and women
Average age and age range		Average age and age range
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =) Comparator (n =)	<ul style="list-style-type: none"> · Number of people randomised to this group · Intervention name · Comparator name · Specify whether phacoemulsification, or other intervention, performed at same time as intervention 	ECP surgical parameters, <i>e.g. degrees of ciliary epithelium treated, laser power</i> Comparator parameters, <i>e.g. dosage of drugs</i>
Outcomes		
Primary and secondary outcomes <i>as defined in study reports</i>	<ul style="list-style-type: none"> · IOP at baseline · IOP at follow-up · Number of glaucoma medications at baseline · Number of glaucoma medications at follow-up · Intraoperative complications · Postoperative complications or secondary surgery · Duration of follow-up · Loss to follow-up · Intervals at which outcomes assessed Adverse events reported (Y/N)	Planned/actual length of follow-up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: <i>(if applicable)</i> Date of publication
Sources of funding		Reported subgroup analyses (Y/N) Were trial investigators contacted?
Declaration of interest		

CONTRIBUTIONS OF AUTHORS

Marta Toth, Kuang Hu and Catey Bunce wrote the protocol. All authors reviewed and approved the protocol.

DECLARATIONS OF INTEREST

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